REMARKS

Claims 20-43 were pending. In response to a Restriction Requirement, Applicant selected Group 1 with traverse. The election is treated by the Examiner as an election without traverse. Examiner indicated that claims 20-35 and 37-43 are drawn to the elected invention and would be examined. Claims 20-35 and 37-43 stand rejected.

Claim 25 is cancelled. Claims 20-24, 26-35 and 37-43 are under examination and pending. Claims 26 and 39 have been amended.

Item 3a. Double Patenting.

Claim 25 stands rejected under 35 U.S.C. §101 as claiming the same invention as claim 4 of U.S. Patent No. 6,077,949.

Claim 25 has been cancelled.

Item 3b. Obviousness-type Double Patenting

Claims 20-35, 37, and 41-43 stand rejected on the ground of obviousness-type double patenting as unpatentable over claims 1, 2, 3, 4, 7, 8, and 9 of Patent No. U.S. 6,077,949, as not patentably distinct.

Applicant is filing a Terminal Disclaimer over U.S. Patent No. 6,077,949 with this Amendment. In view of the Terminal Disclaimer, Applicant respectfully requests withdrawal of the rejection for obviousness-type double patenting.

For the convenience of the Examiner, Applicant is submitting a copy of a Revocation and Power of Attorney previously filed on October 11, 2006. See attached.

Item 4a. Rejections under 35 U.S.C. §112(1)

Claims 20, 27-35, and 37-43 stand rejected as not reasonably providing enablement for a mammalian homolog or variant of the polypeptide of SEQ ID NO:12, or a polypeptide which has at least 80%, 90%, or 95% sequence identity and which selectively binds to the GLP-2 receptor.

Applicant respectfully suggests that the structures of the isolated polynucleotides which encode the claimed forms of the GLP-2 receptor are extensively supported in the specification. At the outset the specification makes clear that the GLP-2 receptor has "structural features common to the G-protein receptor class, including seven transmembrane regions." Page 3, lines 29-31.

With regard to structural homologs, figure 9 compares the amino acid sequence of rat and human GLP-2 receptors and indicates positions in the sequence in which the amino acids are conserved, those in which the amino acids are conservatively related, and those in which the amino acids are unrelated.

The structure is further limited in that the homologs and variants of claim 20 must retain the structural qualities of a GLP-2 receptor, including: (1) a transmembrane domain spanning residues 181-203 inclusive, (2) another transmembrane domain spanning residues 211-230, (3) another transmembrane domain spanning residues 262-285, (4) another transmembrane domain spanning residues 300-321, (5) another transmembrane domain spanning residues 339-362, (6) another transmembrane domain, spanning residues 386-405, and (7) a transmembrane domain spanning residues 422-441. (All sequence position numbering is according to SEQ ID NO:12.) Page 5, lines 18-28. The intracellular domain is thought to span residues 442-553. Page 6, lines 20-21.

The person of ordinary skill in the art wishing to construct variants of GLP-2 receptor in accordance with claim 20 would also be guided by the specification at page 14, line 29 to page 15, line 10, which discusses limitations in changes to the loops connecting the transmembrane domains.

The specification provides further structural constraints on the variants in that particular regions of the sequence are identified as extracellular loops, including amino acid residues corresponding to 401-509 of SEQ ID NO:2 and 65-180 of SEQ ID NO:12. Page 18, lines 12-14. Moreover, loops at residues 363-385 and 442-533 are intracellular. *Id.* at lines 14-15.

With the above considerations in mind, one of skill in the art wishing to make a variant GLP-2 would recognize that about 15% of the residues are non-conservative sites and that some of these would be of little interest based on the structural constraints identified above.

In addition, the specification provides a specific example useful to one of skill in the art wishing to construct a variant GLP-2. As noted by the Examiner, a nucleotide substitution resulting in Glu^{85}-GLP-2 receptor results in expression of an active receptor. Page 10, lines 8-13.

As claim 20 is directed to "a GLP-2 receptor" the function of the variant GLP-2 receptor is also important. An assay for a receptor activity in elevating cyclic AMP levels is provided on Page 26, lines 22-27. Consequently, one of skill wishing to evaluate variants of GLP-2 receptor could readily determine the activity of a construct after transfecting a Cos-1 cell. See example 2.

With regard to claim 27, the Examiner states that the specification does not disclose a polypeptide that shares the recited percent identity with SEQ ID NO:12. Claim 27 requires "at least 95% identity." In contrast to the Examiner's assertion, the specification identifies a functionally active hGLP-2 variant having about 99% identity. Page 10, lines 8-15.

With regard to claims 41 to 43, which require at least 80%, 90% and 95% nucleotide identity, respectively, to nucleotides 320-1780 of SEQ ID NO:11, Applicant respectfully points to figure 9. Inspection of figure 9 shows that the rat sequence has about 82% identity to hGLP-2 receptor over the relevant residues. Because nucleic acid sequence homology is generally less than that of the corresponding amino acid sequence, one of skill in this art would find that the disclosure enables the range of variability claimed. Moreover, the specification reports that "the partial human GLP-2 receptor cDNA (HHT13) is highly homologous to rat GLP-2 receptor cDNA at both the nucleotide and amino acid level. SEQ ID NO:9 shows 87.1% identity with the

rat GLP-2 receptor cDNA sequence." Page 29, lines 1-6. The corresponding amino acid sequences have 87.4% identity. *Id.* The specification also recites the desirability of at least 80%, 90%, and 95% sequence identity. Page 7, lines 3-5.

Regarding claims 28-31, the Examiner asserts that the specification does not enable an isolated polynucleotide which hybridizes under un-specified conditions to the nucleic acid of SEQ ID NO:11 that would retain the functional integrity of SEQ ID NO:11.

In contrast to the Examiner's assertion, the designation "high stringency" is a term of art well understood by a worker seeking to hybridize two polynucleotides. Moreover, the specification implicitly defines the term to mean that the conditions identify polynucleotides that are 90% identical, or more. Page 7, lines 4-5. Thus one of skill in the art could select a set of conditions that require 90% identity of polynucleotides for hybridization. A particular set of hybridization and wash conditions is identified on Page 22, lines 12-20, and may be compared to medium stringency conditions which are shown on Page 27, lines 8-14. As described above, Applicant has extensively described sequence domains (in the amino acid sequence) that are highly conserved or that have particular functional correlates. The correspondence between the amino acid and nucleotide sequences, as shown for example in Figures 5 and 6, permit easy matching of these sequence domains with the nucleotide sequences.

Moreover, claims 26-35, and 38-43 incorporate the limitations of the claims from which they depend. For all these reasons, the above-mentioned claims are reasonably enabled.

Claims 39-40 stand rejected for lack of enablement of "the infinite number of variants" of GLP-2. The Examiner states that "the specification enables using a cell expressing said nucleic acid (SEQ ID NO:11) to identify ligands for the GLP-2 receptor of SEQ ID NO:12."

Claim 39 has been amended to recite a functional GLP-2 receptor comprising the amino acid sequence of amino acids 67-553 of SEQ ID NO:12. Consequently the rejection of claim 39, and claim 40 which depends from claim 39, is moot, for at least the reasons provided above.

Item 4b. Written Description

Claims 20, 27-32, and 39-43 stand rejected as failing to comply with the written description requirement.

The Examiner finds that the claims do not require that the polynucleotide or encoded polypeptide possess any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are reportedly drawn to a genus of polynucleotides that is defined only by sequence identity.

In contrast to Examiner's statement, the specification provides several recitations of sequences that are in the genus GLP-2 receptor. In particular, the specification shows full length human GLP-2 receptor (Figure 9), full length rat GLP-2 receptor (Figure 9), active truncated human GLP-2 receptor (Page 5, lines 30-31), active truncated rat GLP-2 receptor (Page 5, lines 15-18), and a point mutation variant (Page 10, lines 8-14). Thus, unlike Fiddes, in which a single sequence was shown, the instant specification shows five sequences. Fiddes v. Baird, 30 USPQ2d 1481 (Board Pat. App. Int. 1994). From this disclosure, one of skill in the art can readily determine that some domains are functionally inactive. Moreover, comparison of the rat and human sequence shows conserved regions and residues and variable regions. Furthermore, some specific amino acids can be substituted without degrading the receptor activity.

It is unnecessary and not even desirable to recite every species within the genus because one of skill in the art would recognize from the disclosure of the five species mentioned above that the inventors had possession of the invention. However, the Applicant further disclosed that transmembrane domain I corresponds to residues 181-203, that transmembrane domain II corresponds to residues 211-230, that transmembrane domain III corresponds to residues 262-285, that transmembrane domain IV corresponds to residues 300-321, that transmembrane domain V corresponds to residues 339-362, that transmembrane domain VI corresponds to residues 386-405, and that transmembrane domain VII corresponds to residues 422-446. Page 6, lines 13-17. Moreover, based on the comparison of rat and human sequences in Figure 9, it is apparent that the transmembrane domains tend to be conserved. The specification provides

additional structural information. For example, intracellular domains and extra cellular domains are identified. Thus, in combination with the five exemplary GLP-2 receptor sequences a wealth of structural information is provided to define the invention.

The specification also provides functional characteristics of the GLP-2 receptor genus. Particular structural regions are identified as suitable for use as immunogenic fragments. Page 18, lines 9-16. Also a functional assay was used to demonstrate the stimulation of adenylate cyclase by activated GLP-2 receptor. See Example 2.

The correlation of structure to function was addressed above in which several versions of GLP-2 receptor were found to be active.

Lastly, the Examiner suggests that a specification should show a method of making the claimed product. See Office Action at page 10. The specification provides a step-by-step recipe for isolating "one million cDNA clones" of human GLP-2 receptor. Example 3, particularly page 27, line 18. Other examples show cloning of rat GLP-2 receptor (Example 1) and mouse GLP-2 receptor (Example 1) cDNAs. Comparison of an isolated clone polynucleotide sequence with the several exemplary sequences of the genus by hybridization, sequencing or other techniques is well-known in the art.

Thus Examiner's statement that "the only factor present in the claim is a partial structure in the form of a recitation of percent identity" ignores the extensive description in the specification. Here, the specification provides ample written description to one of skill in the art.

Item 5. Rejection under 35 U.S.C. §112(2)

Claims 20-35, 37-38 and 41-43 stand rejected as indefinite.

Item 5a. The Examiner asserts that there is "no upper limit of how many amino acids to substitute."

All the limitations of the claim must be considered. Applicant respectfully suggests that Examiner's rejection is directed to substitution of amino acids in element (c) of claim 20. The element is limited to a polypeptide of 486 or more amino acids that selectively binds GLP-2 or is a GLP-2 receptor. Thus, the upper limit of amino acids is effectively limited by the requirement to display the necessary function. Moreover, addition of any amino acid or amino acid sequence that destroys human GLP-2 receptor activity is excluded. In practice the possible number of sequences having the core sequence and additional amino acids is further limited because of the structural information provided in the specification and, moreover, will depend on the specific objective of the researcher. For at least these reasons the claim is not patentably indefinite.

Item 5b. Claims 25 and 26 are rejected as indefinite because "it is unclear whether the claim is referring to one polynucleotide which encodes human GLP-2 receptor and one that encodes the amino acid sequence of amino acids 1-553 of SEQ ID NO:12."

Claim 25 has been cancelled and the rejection of claim 25 is rendered moot. Although Applicant maintains that claim 26 was not indefinite, the claim has been amended solely to speed prosecution.

Item 5c. Claims 28-31 are rejected as indefinite in the recitation of "hybridizes under conditions of high stringency."

As explained above, the term "high stringency" is a term of art and no definition is necessary. Indeed as Examiner points out, and as described above, the specification explains that high stringency hybridization corresponds to 90% or more sequence identity. One of skill in the art will recognize hybridization conditions that select for 90% or more identity. As but one example, the specification provides hybridization conditions at page 22, line 16-19.

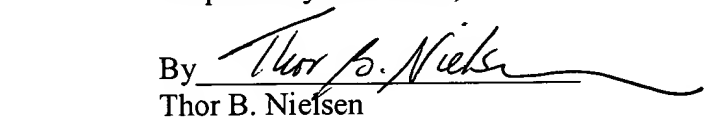
It is believe that we have fully responded to all the Examiner's rejections. Consequently, Applicant respectfully requests withdrawal of all rejections and allowance of pending claims.

An Information Disclosure Statement accompanies this Amendment. Consideration of the references is respectfully requested.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 22-0185, under Order No. 22316-00029-US2 from which the undersigned is authorized to draw.

Dated: November 22, 2006

Respectfully submitted,

By 

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